32. The polynucleotide of claim 20, encoding a protein that contains the mouse Motif T shown in Figure 5.

33. The polynucleotide of claim 20, encoding a protein that contains the mouse Motif 1 and Motif 2 shown in Figure 5.

34. The polynucleotide of claim 20, encoding a protein that contains the mouse Motif A, Motif B, Motif C, and Motif D shown in Figure 5.

REMARKS

This paper is responsive to the Office Action dated February 28, 2002 (Paper No. 31).

Upon entry of this amendment, Claims 5, 9, 20-28 and 31-34 are pending in this application. Claims 5 and 9 are withdrawn; Claims 20-28 and 31-34 are under examination.

Claims 20, 23-26, 28, and 32-34 stand rejected. Claims 21, 22, and 27 are objected to as depending from a rejected base claim. Claim 31 is objected to as depending from a claim that was previously canceled. Upon entry of this paper, the claims will be amended as shown above.

Further consideration and allowance of the application is respectfully requested.

Interview:

The undersigned wishes to express his gratitude to Examiners Sumesh Kaushal and Irem Yucel, and Biotechnology Practice Specialists Brian Stanton and George Elliott, for discussing this application and related matters at an interview at the Patent Office on September 11, 2002, and at other times in the past 5 months by telephone.

Applicants acknowledge with gratitude withdrawal of the rejection of certain claims of this application under 35 USC § 112 ¶ 1 as not being adequately described in the specification.

At the interview at the Patent Office, and in several of the conversations by phone, the representatives of the Office indicated that claim 20 would be put into condition for allowance if it were amended to require that (in addition to the features already present in the claim), the protein have motifs identified in Figure 5. Specific analogy was made to protein kinases, which have a particular motif that apparently cannot be altered without eliminating enzymatic activity. It was suggested that reciting telomerase motifs in the claims of the present application would provide guidance to the

reader wishing to make telomerase variants based on SEQ. ID NO:2, instructing them not to mutate the residues in the motifs.

Applicants' representative has declined to make this amendment as being unnecessary for the practice of the invention, or the patentability of the claimed subject matter, for reasons explained in the following section.

Enablement rejection:

Claims 20, 23, 26, and 32-34 stand rejected under 35 USC § 112 ¶ 1 on the basis that the specification is enabled for an isolated encoding mouse mTERT protein of SEQ. ID NO:2, but not for other natural or non-natural TERT proteins that have at least 90% sequence identity to SEQ. ID NO:2. The Office Action indicates that the specification does not enable the skilled reader to make and use the invention commensurate in scope of the claims. Applicants respectfully disagree for the following reasons:

- The Office has not established a prime facie case for lack of enablement
- Amino acid variants of the representative species (SEQ. ID NO:2) that have telomerase activity can be obtained without undue experimentation
- The Office has an established policy of issuing patents with claims reciting degrees of identity to a representative species
- It would be contrary to the public policy objectives of the Patent Law to limit coverage to just the representative species

A: No prima facie case for lack of enablement:

The Patent Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention[1]. In making this rejection, the Office indicates that the specification fails to provide guidance as to where to alter the representative species, and that the effect of any such alterations is unpredictable.

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[1] *In re Wright,* 27 USPQW2d 1510 (Fed. Cir. 1993). It is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. *In re Marzocchi* 169 USPQ 367, 370 (CCPA 1971). The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. MPEP § 2164.04.

On the contrary: the specification and general knowledge in the art provide considerable guidance as to where alterations may be made. Figure 3 compares the mouse TRT sequence with the human TRT sequence, indicating residues that change between species that the reader may wish to alter. Figures 4 and 5 provide a very thorough analysis of sequences conserved between TRT proteins and other proteins having related function. The reader may wish to avoid altering these motifs when making variants. The skilled reader will also be aware that "conservative" changes (substitution of amino acids with alternatives that have similar polar, non-polar, or aromatic features) will be generally better tolerated. Further information relating to potential functional domains of TRT are found in the preceding applications in this series claiming TRT of other species, which are incorporated into this application by reference.

Having designed a variant of TRT, optionally guided by such information, the user of this invention may then determine whether it falls within the scope of the claim. This requires two determinations. The user needs to determine whether the variant has at least 90% sequence identity to SEQ. ID NO:2. This is easily done, simply by determining the sequence of the variant, and comparing it with SEQ. ID NO:2, as listed in the disclosure.

The user also determines whether the variant telomerase catalytic activity. Section 3, beginning on page 63 of the specification, describes a number of assays for determining telomerase activity: for example, measuring telomere length when TRT is transfected into cells, or measuring extension of telomeric primers by dot blot, reverse transcription, or by the telomerase repeat amplification protocol.

If the variant has both the required degree of sequence identity to SEQ. ID NO:2, and telomerase catalytic activity, it will fall within the scope of the claimed invention.

The rejection made on the Office Action relies on the assertion that it is not possible to predict with absolute certainty which of the variants will work. This assertion is inadequate to support a prime facie case for lack of enablement. Absence of complete predictability only means that the ultimate proving of functional variants is a matter of empirical testing — *not* that such variants are hard to find. Indeed, there are about 22,640 possible variants that have a single amino acid substitution, about 255 million that have two amino acid substitutions, and so on exponentially. A substantial proportion of the variants will have telomerase activity. There is no minimum number of functional variants that are possible in order for the claims to be enabled. Indeed, there is no reason why the skilled reader could not make any number of functional variants that they desire.

B: Variants may be obtained by routine experimentation

There are a number of methods available to construct variants of the TRT sequence. The Office Action implies that the user would want to create variants by making deliberate changes to SEQ. ID NO:2, as described above. Deliberate point mutations are sometimes made when the investigator wants to map functional elements within the primary protein structure.

Although the reader may wish to make variants by mutation at particular sites, it is unnecessary for them to do so. Where the object is only to generate functionally equivalent variants, the skilled reader can employ a random mutation strategy, which is even more straightforward. There is an enormous literature in the art relating to introducing mutations of various kinds. The standard texts *Protocols in Molecular Biology* (Ausubel et al. eds.) and *Molecular Cloning: A Laboratory Manual* (Sambrook et al. eds.) describe techniques employing chemical mutagenesis, cassette mutagenesis, degenerate oligonucleotides, mutually priming oligonucleotides, linker-scanning mutagenesis, alanine-scanning mutagenesis, and error-prone PCR. Other efficient methods include the E. coli mutator strains of Stratagene (Greener et al., Methods Mol. Biol. 57:375, 1996) and the DNA shuffling technique of Maxygen (Patten et al., Curr. Opin. Biotechnol. 8:724, 1997; Harayama, Trends Biotechnol. 16:76, 1998).

The mutated variants can then be cloned out and tested for functionality as described in the specification. To the extent that the user may wish to test variants near the outer limit of variability in the claims (i.e., only ~90% identical to SEQ. ID NO:2), they may subject the representative sequence to successive cycles of mutation and functional testing — or choose a mutation strategy that generate more abrupt changes, such as the DNA shuffling technique.

To what extent will the variants produced by these techniques have the required functional activity? The Office Action cites *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, USPQ 81 (Fed. Cir. 1986), and *In re Wands*, 8 USPQ2d (Fed. Cir. 1988) as setting the standard for unreasonable experimentation. Indeed, in both these cases, the patent under consideration was found to be *enabling* for production of the genus of monoclonal antibodies having the specificity and affinity claimed[2]. The

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[2] In *Wands,* the patent application claimed monoclonal antibodies of a particular specificity and affinity. The PTO contended that only 2.8% of the hybridomas obtained were proven to fall within the claim, and thus the claim was not enabled. *The Court held that the application was fully enabled for the claimed subject matter,* because it was standard practice to screen negative hybridomas in order to find one that makes the desired antibody. 8 USPQ2d at 1406-07.

screening of TRT variants for function according to the present invention is routine in the same manner as testing hybridoma clones for secretion of antibody with particular characteristics.

Applicant does not dispute that some variants of SEQ. ID NO:2 will have less telomerase catalytic activity than the prototype sequence. However, there are many reasons to believe *a priori* that variants of SEQ. ID NO:2 having the required function will be easy to find.

1. The comparison of mouse TRT to human TRT in Figure 3 shows that they are only ~70% identical. Yet, both molecules demonstrate telomerase activity in the TRAP assay, and extend proliferative capacity when transfected into mammalian cells. This means that *at least 30% of the sequence is tolerant to amino acid substitution.* Random mutation strategies will readily place neutral amino acid changes into these and other regions of the molecule.

2. Some parts of the TRT protein are completely dispensable without eliminating telomerase activity. Enclosed with this Response is issued U.S. Patent 6,337,200. The patent describes and claims functional variants of human TRT that comprise deletions of residues 192-323, and 415-450 of the 1132 amino acid sequence. If large portions of the sequence can be deleted without eliminating telomerase catalytic activity, then surely these regions will be tolerant to amino acid substitutions of considerable scope.

3. Even conserved motifs in DNA polymerase enzymes are not required for functional activity. Enclosed with this Response is an article by Patel & Loeb (Proc. Natl. Acad. Sci. 97:10, 5095), entitled "DNA polymerase active site is highly mutable". The article describes experiments in which mutations were introduced into the 13 amino acid "motif A", known to be within the catalytic site of the polymerase. After functional selection for variants retaining activity, 12 of the 13 residues of the motif were found to be mutable without deleting wild-type activity. A wide variety of amino acid substitutions was obtained at sites that are conserved between different bacteria. Some positions permitted as many as 10 different substitutions (Fig. 3). A mutant was obtained with wild-type DNA polymerase activity that had *six* amino acid substitutions within the motif (Fig. 2).

By analogy, the conserved motifs in TRT are useful in identifying natural homologs and mapping functional relationships. The reader may wish to avoid altering motifs when making variants. But it is anticipated that the motifs in TRT will still be tolerant to a substantial range of alterations without eliminating telomerase catalytic activity.

The Office has invited applicants to place telomerase motifs within the limitations of the claims, as a way of placing the claims in condition for allowance. It is respectfully submitted that this is unnecessary. As indicated in the Patel & Loeb article, motifs of this type in other DNA polymerase enzymes may readily be altered without eliminating enzyme function. Since the Office contends that claim 20 as currently presented is not enabled by the specification, it is difficult to understand how reciting the motifs within the claims would thereby render the claims enabled, as the Office suggests[3].

In summary, generating variants of the representative sequence can be done by standard techniques in the art. The variants can be tested for functionality by a number of suitable assays, such as those described in the specification. The evidence of record in this application and presented in this Response implies that a substantial proportion of these variants will have telomerase catalytic activity, and can be made and identified without undue experimentation.

C: The Office has an established policy of allowing coverage for closely related sequences

The "Revised Interim Written Description Guidelines" of the U.S. Patent & Trademark Office promulgated on March 7, 2000 indicates that claims to molecules related by sequence identity fall within the description requirements of 35 USC § 112 ¶ 1. Example 14, "Product by Function", provides an explicit illustration. The claim at issue is the following:

A protein having SEQ. ID NO:3 and variants thereof that are at least 95% identical to SEQ. ID NO:3 and catalyze the reaction of A → B.

[3] To the extent that the motifs may provide guidance to the reader wishing to make deliberate changes within the sequence, it is not necessary to place the motifs in the claims, since this guidance already exists within the specification.

Example 14 concludes by indicating that the claim should be patentable under the written description requirements of § 112 ¶ 1. Included in the commentary is the following analysis:

- There is actual reduction to practice of the single disclosed species.
- The procedures for making variants of SEQ. ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ. ID NO:3 which have 95% identity to SEQ. ID NO:3 and retain its activity are conventional in the art.

In other words, even though only a single species was actually made, the underlying disclosure is enabling for the production of variants of SEQ. ID NO:3 with the catalytic function recited in the claim.

It is inconceivable that the Office would have promulgated these Written Description Guidelines knowing that this illustration complied with the description requirements of § 112 ¶ 1, but not the enablement requirements of the very same statute.

The present application is extremely rich in the guidance it provides for making variants:

- Pages 49-51 provide a number of methods for making mutant sequences, citing several contemporary reference works and giving illustrations.
- Pages 85-86 provide a description of conservative amino acid substitutions which are believed less likely to affect protein function.
- Figure 3 compares the mouse telomerase protein sequence (SEQ. ID NO:2) with the human sequence, indicating which residues have been changed during evolution while retaining function.
- Pages 22-24, and Figures 4 and 5 provide an extensive analysis of more highly conserved residues, falling within certain motif arrangements shared with telomerase enzymes of other species.
- Pages 63-69 provide a number of assay methods for determining whether the variants have the required function.

It is hard to imagine what else would have been present in the disclosure of Example 14 of the Written Description Guidelines that does not appear in the disclosure of the present patent application.

The Table below shows the number of U.S. patents issued as of September of 2002, having claims that define the scope of biological compounds by a percentage of sequence identity or homology to a representative sequence. There are over 1,000 patents with subject matter defined by a degree of relatedness to a representative species. *Over 300 issued patents have claims to 90% sequence identity or homology.*

TABLE 1: Number of Issued U.S. Patents
with Claim Scope Determined by Identity to Representative Sequence

Percentage	Identical to Representative Sequence	Homologous to Representative Sequence
99%	36	9
98%	38	6
97%	90	9
96%	3	3
95%	374	54
91% to 94%	7	2
90%	276	92
85%	56	21
80%	169	73
75%	50	15
70%	98	73
60% or 65%	38	23
50% or 55%	23	23
40% or 45%	10	5
30% or 35%	6	4
20% or 25%	6	1
Total	765	275

In view of the established policy of the Patent Office that claims reciting sequence identity are patentable, as indicated in Example 14 of the Written Description Guidelines (and in view of the surfeit of patents issued in conformity with this Example), it would be unfair to require more from the owners of the present patent application — either in terms of the content of the disclosure, or additional limitations in the claims.

D: Public policy aspects of the enablement requirement

To the extent that there is latitude available to interpret the enablement requirement, the public policy objectives of the Patent Law obligate the Patent Office to provide adequate protection for the owners of an important invention.

The Office Action questions whether applicants should have the right to obtain claims that encompass any natural telomerase reverse transcriptase protein that is non-identical but closely homologous to SEQ. ID NO:2. The mouse TRT protein contains 1122 consecutive amino acids. It is expected that proteins of this length will have several allotypic variants within the species from which it is obtained. The contribution to the art made by this disclosure is a novel sequence that is representative of a new class of proteins in this species. Given the representative sequence, it is a routine matter to extract TRT cDNA from other expression libraries, which may incidentally contain allotypic differences. Surely applicants are entitled to generic coverage for mouse TRT, without having to determine every naturally occurring allotype in every mouse on the planet.

The Office Action also questions whether applicants should have the right to obtain claims that encompass non-natural TRT proteins that are at least 90% identical to SEQ. ID NO:2. The discovery and sequencing of the TRT family is the result of a lengthy and resource-consuming collaboration between renowned scientists working for the two assignees of this application. The TRT family is an important discovery with implications for drug discovery, cancer treatment, and regenerative medicine. Now that this representative sequence has been disclosed to the public, it is a trivial matter to generate functional variants, using any of the manners described earlier.

It would be unfair to hold applicants to only the exact sequence obtained. This would give competitors an easy way to steal the essence of applicants' discovery simply by making a close functional variant with one or more mutations in the sequence. The objective would be not to improve the properties of the molecule, but simply to evade applicants' patent protection. If this were the general policy of the patent system, it would take away the incentive for researchers to undertake

fundamental discovery research. Instead, it would reward companies that steal other people's finished inventions.

It is also unfair to hold applicants to particular aspects of the sequence (such as motifs) that are not known to be required for function, and are not required to distinguish the invention from the prior art. As indicated in the Patel & Loeb article, even closely conserved motifs may be highly tolerant to mutation without affecting activity. To insist that applicants recite such features in their claims would provide a disincentive to future applicants against putting a full and complete discussion of structural features into their disclosure.

Applicants respectfully submit that the issuance of patents with coverage defined by relationship to a representative species is consistent with the public policy objectives of patent law. It accords the owners of important inventions a claim scope that covers easily obtained variants and work-arounds. Not all disclosures will be entitled to the same scope of coverage. An appropriate scope should be determined by a variety of considerations, such as importance of the invention, closeness of prior art, fullness of disclosure made in the application, and arguments made during prosecution. While this may not be an easy determination, surely it is the responsibility of the Patent Office to do so, rather than to hold applicants to a narrow scope of coverage that does not adequately protect their invention.

Applicants also submit that the specification of this application is relatively rich in describing features of the structure, compared with other patents and patent applications for novel proteins and gene sequences. Accordingly, applicants are entitled to patent coverage for sequences that are 90% identical to the representative sequence, in conformity with established Patent Office practice.

Withdrawal of this rejection is respectfully requested.

Other rejections:

Claims 21, 22, and 27 stand objected to as depending from a rejected base claim. These claims have now been recast as independent claims, incorporating the limitations of the claims upon which they were previously dependent. Accordingly, these claims are believed to be in condition for allowance.

Claims 23-25 stand rejected under 35 USC § 112 ¶ 1 as being enabled for an isolated cell, but not for the subject matter that is claimed. The Office Action argues that the claim reads on cells produced by gene therapy, which it asserts is a highly experimental area of research.

Applicants disagree. Claims 23-25 as previously presented require only that the cell "contain" the polynucleotide, not that they express it or generate any particular therapeutic result. Methods for delivering polynucleotides into cells both in vitro and in vivo are well known in the art and discussed in the specification, which is sufficient to meet the enablement requirement. Furthermore, there is data confirming that administering telomerase in vivo can increase proliferative capacity of cells and have a therapeutic benefit. See, for example, U.S. Patent Application 10/143,536.

Nevertheless, to advance prosecution of the application, claims 23-25 are herein amended to indicate that the polynucleotide is transfected into an isolated cell. Applicants reserve the right to reintroduce claims to anything previously claimed or disclosed in the specification at a later time.

Claim 28 stands rejected under 35 USC § 112 ¶ 1 as reading on a transgenic mouse. The Office Action indicates that the specification fails to disclose a single founder animal that exhibits the required phenotype.

Applicants respectfully disagree. The claim as previously presented does not require that the cell (or an animal containing the cell) have a particular *phenotype*. It requires that the cell has the *genotype* of an altered TERT gene. The principles of making mice having gene knockouts is well known in the art. Mice having an alteration in a particular gene can be made according to standard established techniques, providing: a) the practitioner has possession of the gene being targeted; b) removing the gene does not prohibit viability of the animal. The specification provides the sequence of the mouse TRT gene. The specification also asserts that knockout animals can be made. The 37 CFR § 1.132 Declaration by Choy-Pik Chiu filed with the last Response provided evidence that knockout animals have been made in the manner described in the specification, confirming that the TRT gene is not required for viability of the mouse.

Nevertheless, should the Office indicate that this application is otherwise in condition for allowance, applicants will consider the advisability of amending this claim so as to render this rejection moot. Applicants reserve the right to reintroduce claims to anything previously claimed or disclosed in the specification at a later time.

Withdrawal of all these objections is respectfully requested.

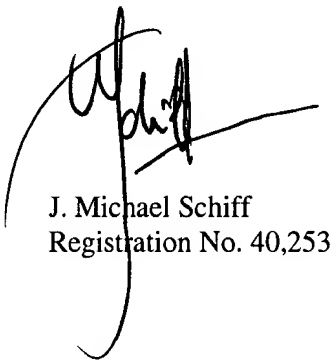
Conclusion

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Office determines that there are still outstanding issues to be resolved before allowance of the application, applicants hereby request an interview by telephone.

Should the Patent Office determine that an extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Assistant Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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November 27, 2002

Version with Markings to show

CHANGES MADE

USSN 09/042,460
Docket 019/224p

Amendments to Claims:

20. An isolated, purified or recombinant polynucleotide encoding a telomerase reverse transcriptase protein, wherein said protein:

    (i) has at least 90% sequence identity to SEQ. ID NO:2; and,

    (ii) has telomerase catalytic activity when associated with telomerase RNA component.

21. ~~The polynucleotide of claim 20, wherein the encoded telomerase reverse transcriptase protein has an~~
    An isolated, purified or recombinant polynucleotide encoding a telomerase reverse transcriptase protein having the amino acid sequence of SEQ. ID NO:2.

22. ~~The polynucleotide of claim 21, wherein the polynucleotide has a~~
    An isolated, purified or recombinant polynucleotide comprising the sequence of SEQ. ID NO:1.

23. ~~A cell comprising~~ An isolated cell transfected with the polynucleotide of claim 20 , or progeny thereof.

24. ~~A cell comprising~~ An isolated cell transfected with the polynucleotide of claim 21 , or progeny thereof.

25. ~~A cell comprising~~ An isolated cell transfected with the polynucleotide of claim 22 , or progeny thereof.

26. An expression vector comprising the polynucleotide of claim 20.

27. An expression vector comprising the polynucleotide of claim 21.

28. A mouse cell in which an endogenous mTERT gene in the cell has been mutated by recombinant means, or progeny of said cell.

31. The polynucleotide of claim ~~1~~ 20, encoding a protein that contains at least 10 consecutive amino acids of SEQ. ID NO:2.

32. The polynucleotide of claim 20, encoding a protein that contains the mouse Motif T shown in Figure 5.

33. The polynucleotide of claim 20, encoding a protein that contains the mouse Motif 1 and Motif 2 shown in Figure 5.

34. The polynucleotide of claim 20, encoding a protein that contains the mouse Motif A, Motif B, Motif C, and Motif D shown in Figure 5.

Claims withdrawn from examination:

5. An isolated, purified or recombinant peptide encoded by the nucleic acid of claim 1.

9., An isolated, purified or recombinant antibody, specifically immunoreactive under immunologically reactive conditions, to the protein of claim ~~6~~ 5.